48. The Structure of the Alkaloid Peduncularine

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Summary

The revised structure **1** is put forward for peduncularine, the main alkaloid of *Aristotelia peduncularis* (Labill.) HOOK. F. *(Elaeocarpaceae)*, on the basis of its spectroscopic properties and those of its degradation products, the *Hofmann* base **3** and the hydrogenation product **4**. Structure **1** represents the relative configuration of the alkaloid.

Peduncularine belongs to the class of indole alkaloids with a monoterpene unit as the aliphatic portion. To our knowledge it constitutes the first example in which an isopropyl group has become detached from the terpene unit and occurs as a substituent on nitrogen.

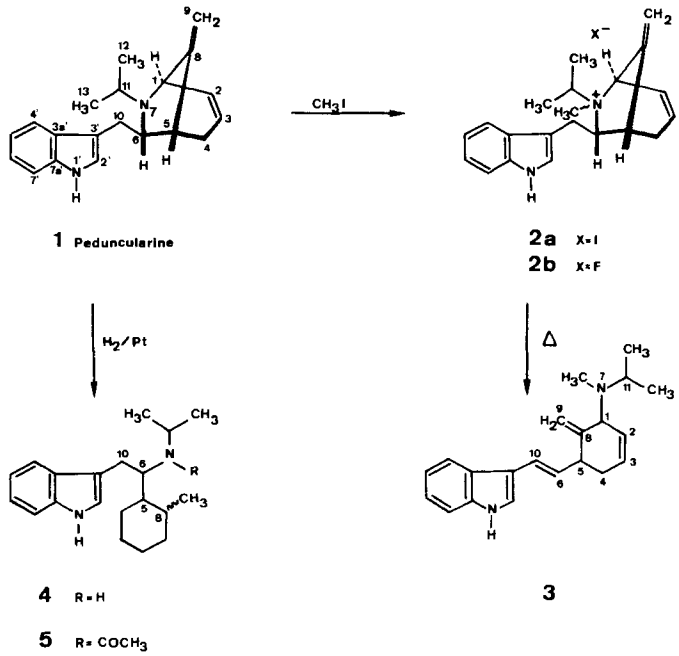
Peduncularine (**1**) is the principal alkaloid of the plant *Aristotelia peduncularis* (Labill.) HOOK. F., which belongs to the *Elaeocarpaceae* and is endemic in rain forests on the island of Tasmania, Australia, where it grows as a straggling bush to the height of *ca.* 2.5 m. Alkaloids have been obtained from a number of other *elaeocarpaceous* plants (mostly from New Guinea) [2], but also from *A. serrata* (New Zealand) [3] and *A. chilensis* (Chile) [4].

Peduncularine was first isolated by *Bick et al.* [5], who ascribed to it an indole-pyrrolizidine structure on the basis of spectroscopic evidence. An alternative structure proposed by *Joule* [6] was in good agreement with the isoprene rule, although it did not accord with the spectroscopic data; in the event, however, the simple isoprene rule has proved an unreliable guide to the structure of peduncularine.

[1]) No. 171: [1].

[2]) Part of dissertation to be presented by *H.-P. R.*, Universität Zürich and of diploma project of *R. K.*, Universität Zürich.

Scheme 1

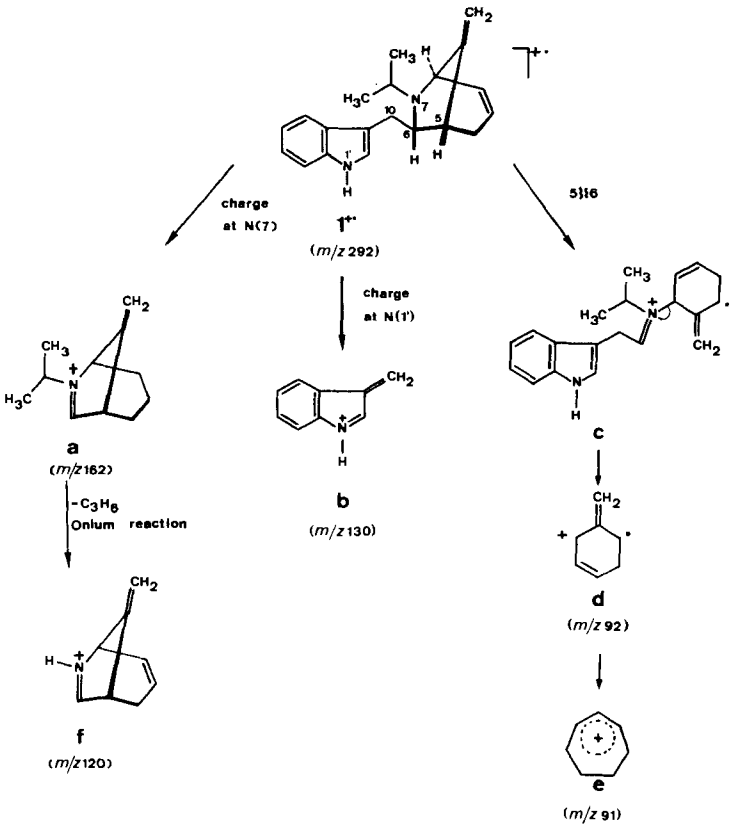


We have since obtained further chemical and spectroscopic evidence, in particular ^{13}C-NMR. data not available at the time of the initial isolation, which have shown that both the above-mentioned structures are untenable. In their place we put forward structure **1** [7], which has been confirmed by degradative experiments; this structure is moreover in complete accord with all the spectroscopic data.

Peduncularine (**1**, *Scheme 1*, Mol.-Wt. = 292, $[\alpha]_D^{19} = -24°$ (CH_3OH), $[\alpha]_D^{21} = -76°$ ($CHCl_3$)) has a 3-substituted indole chromophore, as shown by colour reactions and by UV., ^{1}H-NMR. and ^{13}C-NMR. spectra (see exper. part). The mass spectrum of **1** is dominated by the base peak at *m/z* 162 (in the low voltage spectrum this is the only fragment ion peak). The corresponding ion **a** is formed by cleavage of the doubly activated C(6)–C(10) bond *(cf. Scheme 2)*. If the charge is located on the less basic indole nitrogen atom, cleavage of this bond results in the fragment *m/z* 130 (**b**) characteristic for indole derivatives [8]. The fragment *m/z* 144 is lacking; this ion is likewise typical of indoles, and its absence shows that the indole residue is not 2,3-disubstituted. A third fragmentation, directed by N(7), leads to **e** (*m/z* 91) *via* the ions **c** and **d**. The ion **f** (*m/z* 120) arises by loss of propene from **a**.

In the ^{1}H-NMR. spectrum (360 MHz), the *s* at highest field in the aromatic region (6.93 ppm) corresponds to the H–C(2′) proton of the indole residue, and there is no signal for an H–C(3′) proton, which should resonate at distinctly higher field; this position is thus substituted. There is only one proton exchangeable with D_2O, which corresponds to the indolic H–N; the aliphatic N atom is evidently tertiary. Apart from the remaining protons in the indolic residue and 2 vinylidene

Scheme 2



protons (2*s* at 4.94 and 4.81 ppm), the following structural sequences can be established:

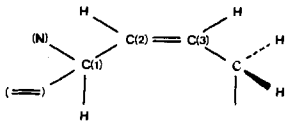
A) *N*-Isopropyl-group: H–C(11) forms a *septet* at 3.02 ppm and is coupled to 2 methyl groups (*d* at 1.32 and 1.17 ppm collapsing to 2*s* on irradiation at 3.00 ppm). Furthermore, ^{1}H-NMR. experiments with Eu(fod)$_3$[3]) revealed a large displacement of the methine proton signal on gradual addition of the reagent, approximately equal to the magnitude of shift of protons H–C(1) and H–C(6), which are likewise attached to carbon atoms *α* to a nitrogen atom. Protons on a *β*-carbon atom, H–C(5), 2 H–C(10), and the methyl protons of the isopropyl group 3 H–C(12) and 3 H–C(13) moved at a slower rate comparable with one another, while the remaining protons were shifted even more slowly and to a similar extent to one another, except for the carbocyclic indole protons which were practically unaffected.

B) A second sequence $H_2C(10)$–HC(6)–N(7) was established as follows: from their chemical shifts, the protons on C(10) are allylic, H_a–C(10) 2.97, and H_b–C(10) 2.69 ppm. H–C(6) is attached to N, 2.90 ppm. H_a–C(10) overlaps in

[3]) = Tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-dionato-4,6]-europium.

part with the *septet* at 3.02 ppm. There is a geminal coupling of 14 Hz between H_a and H_b, a coupling of 11 Hz between H_a and H–C(6), and one of 3 Hz between H_b and H–C(6). These 3 protons gave no evidence of being coupled to any others; in particular, H–C(6) and H–C(5) are not coupled, which indicates a dihedral angle of 90°; thus the methylindole group is substituted *exo* to the bicyclic nucleus.

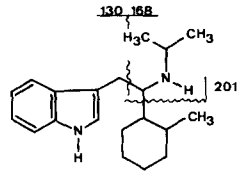
C) The third sequence comprises



H–C(1) is diallylic and adjacent to N; it resonates at 3.85 ppm (*d*, $J=6$ Hz) and is coupled to H–C(2) (decoupling experiment) which in turn shows a *cis* coupling ($J=8$ Hz) to H–C(3). The latter is weakly coupled to one of the 2 protons on C(4) (2.44 and 2.04 ppm), which have a geminal coupling of 18 Hz indicating that the vinylic H–C(3) proton forms approximately equal dihedral angles with those on C(4), *i.e.* the angles between the π orbitals of the double bond and 2 H–C(4) are almost equal and about 30° [9]. A small coupling between one of the hydrogens on C(4) and H–C(5) was detected. This evidence indicates that C-atoms 1, 2, 3 and 4 are coplanar, and thereby supports the bicyclic structure **1**.

The ^{13}C-NMR. spectrum of peduncularine is in accord with structure **1** (see exper. part). In particular, the C(11) signal was identified by a heteronuclear decoupling experiment in which the H–C(11) proton was irradiated; since the latter signal is overlapped by the H–C(6) multiplet in the ^{1}H-NMR. spectrum, both the C(11) and C(6) doublets in the ^{13}C-NMR. spectrum were decoupled, but the 2 could easily be distinguished by comparison with the model compound *N*-isopropylpyrrolidine (N–*C*H(CH$_3$)$_2$: ^{13}C-NMR. ($CDCl_3/CD_3OD$ 17:3) $\delta=$ 55.1 ppm). These observations confirm the presence of an *N*-isopropyl group in **1**. On treatment with CH_3I, **1** formed the methiodide **2a**, which was converted into the methofluoride **2b** by ion exchange. Pyrolysis of **2b** gave a 41% yield of the *Hofmann* base **3** (M = 306) whose UV. spectrum corresponded with that of 3-vinylindole [11]; 2-vinylindole derivatives give distinctly different UV. spectra [12].

The base peak in the mass spectrum of **3** is *m/z* 234 ($C_{17}H_{16}N$); the corresponding ion has lost one nitrogen atom [N(CH$_3$)CH(CH$_3$)$_2$ group], which is a further indication of the presence of an *N*-isopropyl group in **1**. The structure of **3** was confirmed by its ^{1}H-NMR. spectrum (360 MHz): in addition to the new *N*-methyl substituent (2.21 ppm, *s*), the *N*-isopropyl group could be detected by signals at 3.04 (*septet*, H–C(11)), 1.08 and 1.07 ppm (2*d*) (decoupling experiment). The presence of the newly-formed C(6)–C(10) double bond with breaking of the original C(6)–N bond was demonstrated by signals at 6.57 (*d*, $J_{trans}=16$ Hz) and 6.40 ppm ($d\times d$, $J_{trans}=16$, $J_{H-C(5),H-C(6)}=8$ Hz); irradiation at 3.14 ppm (H–C(5)) reduced the signal at 6.40 ppm to a *d* ($J=16$ Hz). As before, H–C(5) is coupled to 2 allylic protons (2 H–C(4), 2.45–2.10 ppm). The proximity of H–C(6) and H–C(5), which could not be directly observed in **1** through lack of coupling, is evident in the degradation product. There was no shift of double bonds during the pyrolysis, since 4 olefinic protons are present (2 as part of CH_2=C), and



4

H–C(1) is still diallylic and next to the aliphatic nitrogen atom ($\delta = 4.02$ ppm, br. *s*).

The catalytic hydrogenation (H_2/PtO_2) of peduncularine (**1**) in glacial acetic acid gave a 65% yield of 1,2,3,7,8,9-hexahydro-1,7-secopeduncularine (**4**, M = 298)[4]). In addition to the hydrogenation of the 2 C,C-double bonds, the doubly allylic C(1)–N(7) bond has been hydrogenolyzed. The mass spectrum shows 3 characteristic fragmentation peaks (*m/z* 130, 168, 201) which support structure **4**. The ion *m/z* 201 further demonstrates the presence of the C(6)–N(7) bond in **1**. In the ^{1}H-NMR. spectrum of **4**, the region between 6.8 and 3.5 ppm is devoid of signals. An additional methyl signal is at 0.87 ppm (*d*), and 2 signals (br. *s*, 8.23 and 1.75 ppm) which disappear on D_2O exchange, show the presence of 2 H–N groups. Furthermore, **4** has been characterised by its *N*(7)-acetyl derivative **5** (M = 340).

The structure **1** thus derived for peduncularine represents the relative configuration. It can be inferred that it is built up from tryptamine and a monoterpene unit by the plant; the adduct formed initially must then undergo a rearrangement in which the isopropyl group is transferred from the terpene unit to the nitrogen.

We thank the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung,* and the *Australian Research Grants Committee,* whose support has made this work possible. We are also grateful to *Siegfried AG,* Zofingen, for help in working up the methanol extract; to Dr. *W. Schwotzer,* Zürich, and Dr. *A. Jones,* National NMR. Centre, Canberra, for NMR. spectra; to Mr. *C. Macdonald,* C.S.I.R.O., Canberra, Dr. *J. Macleod,* A.N.U., Canberra, Dr. *A. Lorenzi* and Mr. *N. Bild,* Zürich, for mass spectra; to Dipl. chem. *E. Schöpp* for HPLC. work; to Dr. *E. Browne* for preparation of model compounds, and to colleagues and students of the University of Tasmania for help in collecting plant material. Part of this work was done during study leave in Zürich by one of us (I.R.C.B.), who gratefully acknowledges the interest and kindness of the late Prof. Dr. *H. Schmid* in according hospitality and facilities in his laboratories.

Experimental Part

General. – Evaporations were carried out *in vacuo* (*i.v., ca.* 16 mbar) with a rotatory evaporator at a maximum bath temperature of 50°; thin-layer chromatography (TLC.) on silica gel HF_{254}; preparative TLC. on *Merck* type 60 PF_{254} silica gel; colour reactions with Ce(IV)sulfate reagent and potassium iodoplatinate reagent [13]; high-performance liquid chromatography (HPLC.) on silica gel (*Merck* Lichrosorb SI 60, 5 μm) with a *Varian* Aerograph 8500 (detection: UV. detector at 280 nm); UV. spectra in 99.5% ethanol, data in nm (log ε); IR. spectra in $CHCl_3$, data in cm^{-1}; sh. = shoulder; mass spectra (MS.) on a *Varian* MAT 711, data in *m/z* (rel. %), high resolution by the peak-matching procedure; NMR. spectra in $CDCl_3$ unless otherwise specified, chemical shifts in ppm relative to

[4]) Because of the low intensity of its M^+ in the electron impact spectrum, this value was determined by field desorption mass spectrometry.

tetramethylsilane as internal standard (= 0 ppm), coupling constants (J) in Hz; s = singlet, d = doublet, t = triplet, qa = quartet, m = multiplet; br. = broad.

1. *Isolation.* Whole plant material (184 kg) was collected at Cockle Creek (Tasmania) in mid-November 1977, and passed directly through a compost shredder. The shredded material was dried for a week at 25°, then ground to a coarse powder (95.1 kg) in a *Wiley* mill and extracted in glass percolators with CH_3OH at 20° until the extract gave a negative test with *Mayer*'s reagent. The solvent was evaporated under reduced pressure below 40°, and the extract was finally concentrated to a thick tar (8.3 kg). This crude extract was worked up in batches, a typical procedure being as follows: 1 kg crude material was stirred with 5 l water and 375 ml glacial acetic acid, then allowed to stand for 1 h. The liquid phase was decanted and the residue filtered off. The filtrate was basified with 1 l 25% NH_4OH to pH 10, and the resulting suspension was refiltered. The aqueous solution was extracted with 5% aq. sulfuric acid (400, 300, 200 and 200 ml). The acid extract was again basified with 230 ml 25% NH_4OH-solution and extracted with $CHCl_3$ (300 and 200 ml). The organic extracts were combined and dried (Na_2SO_4); after the solvents had been removed, 1.53 g of residue was obtained. The total yield of crude alkaloid from the extraction of the plant material amounted to 8.3 g.

The crude bases were purified first by column chromatography: 7.3 g were chromatographed on silica gel (*Merck* 60, particle size 0.063–0.2 mm., 350 g; eluent: cyclohexane/$CHCl_3$/ethyl acetate/triethylamine 9:6:4:1). The main fraction contained 1.22 g peduncularine, and a number of other fractions containing minor alkaloids were obtained; these are under study.

2. *Peduncularine* (*6-Exo-(3'-indolylmethyl)-7-isopropyl-8-methylene-7-azabicyclo[3.2.1]oct-2-ene*, **1**). M.p. 155–157° (colourless crystals from $CHCl_3$; [5]). – Ce-sulfate: light blue, rapidly becoming pale, light yellow after 2 min at 100°; K-iodoplatinate: violet. – $[\alpha]_D^{19} = -24°$ (CH_3OH, $c = 1.2$ [5]), $[\alpha]_D^{21} = -76°$ ($CHCl_3$, $c = 2.33$). – UV.: λ_{max} 223 (4.51), 281 (3.77), 290 (3.71); λ_{min} 244 (3.14), 287 (3.68); sh. 274 (3.73). – IR.: 3490 (HN), 2990 (HC), 1690 (C=C), 1620 (C=CH_2), 1490, 1460 (ar.), 895 (C=CH_2). – ^{1}H-NMR. (360 MHz): 8.24 (br. s, 1 H–N, disappears on addition of D_2O); 7.60 (d, $J \approx 7$, H–C(4')); 7.31 (d, $J \approx 8$, H–C(7')); 7.18 and 7.11 (2 t, $J \approx 7$, H–C(5'), H–C(6')); 6.93 (s, H–C(2')); 5.94 (m, H–C(2)); 5.67 (br. d, $J \approx 8$, H–C(3)); 4,94 and 4.81 (2s, 2 H–C(9)), 3.85 (d, $J = 6$, H–C(1)); 3.1–2.85 (m, 1 H–C(10), H–C(6), H–C(11), see theoretical part); 2.8–2.5 (m, 1 H–C(10), see theoretical part); 2.49 (br. s, H–C(5)); 2.48–2.40 ($d \times m$, $J = 18$, 1 H–C(4)); 2.08–2.00 ($d \times m$, $J = 18$, 1 H–C(4)); 1.32 and 1.17 (2 d, $J = 6$, 3 H–C(12), 3 H–C(13)). – Decoupling: Irradiation: 5.67 → 5.94 (s with fine structure) + 2.48–2.40 (sharpening); 3.85 → 5.94 (d, $J \approx 8$); 3.00 → 2.8–2.5 (change) + 1.32 (s) + 1.17 (s); 2.05 → 5.67 (sharpening); in $CDCl_3/CD_3OD$ 17:3: 5.90 (H–C(3)) → 4.00 (sharpening, H–C(2)) + 2.43–2.60 (sharpening, 1 H–C(4)); 2.82 (H–C(5)) → 2.43–2.60 (sharpening). – ^{13}C-NMR. (25.2 MHz, off-resonance): 149.8 (s, C(8)); 136.1 (s, C(7a')); 130.4 + 128.4 (2 d, C(2) and C(3)); 127.7 (s, C(3a')); 121.8, 121.3, 119.1 + 119.0 (4 d, C(2), C(4'), C(5'), C(6')); 114.8 (s, C(3')); 110.9 (d, C(7')); 101.3 (t, C(9)); 69.9 (d, C(1) [14]); 60.4 (d, C(6) [14]); 50.9 (d, C(11)); 45.9 (d, C(5)); 40.1 (t, C(10)); 34.2 (t, C(4)); 23.6 + 22.7 (2 qa, C(12), C(13)). – MS.: 292 (M^+, 1, $C_{20}H_{24}N_2$), 162 (100, $C_{11}H_{16}N$), 130 (9, C_9H_8N), 120 (30, $C_8H_{10}N$), 91 (27, C_7H_7), 70 (6, C_4H_8N).

$C_{20}H_{24}N_2 \cdot CHCl_3$ (411.806) Calc. C 61.25 H 6.12% Found C 61.3 H 6.4%

3. Hofmann *degradation of peduncularine* (**1**). – 100 mg **1** in 3 ml freshly distilled CH_3NO_2 were treated with 0.5 ml CH_3I. After 2.5 h at 20°, the solvent was removed *i.v.* leaving a lacquer in which **1** could no longer be detected. The peduncularine methiodide (**2a**) was converted into the methofluoride **2b** by ion exchange (CH_3OH/H_2O 1:1; Amberlite IRA-400 (F^-)). The residue was dissolved in CH_3OH, distributed in 9 bulb tubes (5 ml), and the solvent was evaporated *i.v.* so as to give a film as uniform as possible on the internal surfaces. The material was then pyrolysed (metal bath 175°, 0.007 mbar, 3–5 min each time). The clear brown distillates were dissolved in $CHCl_3$, combined and evaporated; 64.5 mg residue. Purification by preparative TLC. (cyclohexane/ethyl acetate/ether/25% NH_4OH-solution 40:40:20:1), followed by HPLC. (170 bar, flow: 400 ml/min.) afforded 41 mg of *Hofmann* base **3**. Viscous oil. – Ce-sulfate: brown. – UV.: λ_{max} 224 (4.42), 258 (4.29), 280 (3.98); λ_{min} 242 (4.09), 272 (3.97); sh. 252 (4.21), 297 (3.80). UV. of 3-vinylindole: λ_{max} 225 (4.4), 258 (4.21), 282 (3.95); inflexions 253 (4.13), 278 (3.94), 289 (3.89), 297 (3.80) [11]. – IR.: 3490 (HN), 1660, 1460, 907. – ^{1}H-NMR. (360 MHz): 8.18 (br. s, HN); 7.89 (d, $J = 8$, H–C(4')); 7.30 (d, $J = 8$, H–C(7')); 7.24–7.10 (m, H–C(2'), H–C(5'), H–C(6')); 6.57 (d, $J = 16$, H–C(10)); 6.40 ($d \times d$, $J = 16$ and 8, H–C(6)); 5.92–5.84 (m, H–C(3)); 5.73 (br. d, $J = 10$, H–C(2)); 5.28 (s, 1 H–C(9)); 5.05 (s with fine

splitting, 1 H–C(9)); 4.02 (br. *s*, H–C(1)); 3.14 (*m* resembling *qa*, H–C(5)); 3.04 (*septet*, $J=6$, H–C(11)), 2.45-2.10 (*m*, including *s* at 2.21, 3 H–C–N(7), 2 H–C(4)); 1.08+1.07 (2 *d*, $J=6$, 3 H–C(12), 3 H–C(13)). - Decoupling: Irradiation 4.00→5.94 (change) +5.05 (*s*) +2.45-2.10 (change); 3.14→6.40 (*d*, $J=16$) +2.45-2.10 (profound change); 3.04→1.08+1.07 (2*s*). - MS.: 306 (M^+, 75, $C_{21}H_{26}N_2$), 291 (26), 235 (56), 234 (100, $C_{17}H_{16}N$), 233 (24), 232 (44), 230 (12), 220 (13), 219 (20), 218 (24), 217 (18), 214 (17), 207 (22), 206 (13), 204 (13), 193 (14), 180 (22), 162 (14), 156 (23), 154 (10), 144 (48, $C_{10}H_{10}N$), 143 (45, $C_{10}H_9N$), 131 (11), 130 (69, C_9H_8N), 125 (14), 119 (29), 118 (89, C_8H_8N), 117 (41, C_8H_7N and C_9H_9, mixture 1:2), 115 (20), 110 (20), 91 (52, C_7H_7).

4. *1,2,3,7,8,9-Hexahydro-1,7-secopeduncularine* (**4**). - 100 mg **1** were hydrogenated in 5 ml glacial acetic acid with H_2 and 21 mg PtO_2 *(Heraeus)* for 18 h. The catalyst was then filtered off, the solution was diluted with 2 ml water, made ammoniacal and extracted with $CHCl_3$. After evaporation of the $CHCl_3$, the residue was purified by preparative TLC. (cyclohexane/$CHCl_3$/ethyl acetate/triethylamine 9:6:4:1); 65 mg oil. - Ce-sulfate: light brown. - UV.: λ_{max} 224 (4.35), 282 (3.67), 290 (3.61); λ_{min} 243 (2.98), 287 (3.60); sh. 275 (3.64). - IR.: 3490 (HN), 2965, 2930, 1580, 1460. - ^{1}H-NMR. (360 MHz): 8.23 (br. *s*, H–N(1')); 7.60 (*d*, $J=8$, H–C(4')); 7.30 (*d*, $J=8$, H–C(7')); 7.16+7.09 (2 *t*, $J=8$, H–C(5'), H–C(6')); 6.93 (*s*, H–C(2')); 3.03 (*d* with fine splitting, $J=10$, 1 H–C(10)); 2.92 (*septet*, $J=6$, H–C(11)); 2.82-2.70 (*m*, 1 H–C(10), H–C(6)); 2.16 (br. *s*, H–C(5)); 1.75 (br. *s*, H–N(7)); 1.50-1.10 (*m*, H–C(8), 2 H–C(1), 2 H–C(2), 2 H–C(3), 2 H–C(4)); 0.99+0.97 (2 *d*, $J=7$, 3 H–C(12), 3 H–C(13)); 0.87 (*d*, $J=7$, 3 H–C(9)). - D_2O exchange: the signals at 8.23 and 1.75 disappear. - MS.: 298 (M^+, < 1, determined by FD.-MS.), 201 (3), 168 (100), 130 (11), 72 (23).

5. *7-Acetyl-1,2,3,7,8,9-hexahydro-1,7-secopeduncularine* (**5**). - A solution of 40 mg crude **4** in 2 ml of distilled acetic anhydride was treated with 30 mg anhydrous sodium acetate and stirred at 20° for 18 h. The remaining acetic anhydride was then removed *i.v.* at 50°, the residue was treated with 7 ml of a 1:1 mixture of aqueous 1.2N NaOH and $CHCl_3$, and extracted with $CHCl_3$. After purification by preparative TLC. (cyclohexane/ethyl acetate/$CHCl_3$/triethylamine 9:4:6:1), 36 mg of **5** (84%) were obtained; viscous oil. - K-iodoplatinate: light yellow. - UV.: λ_{max} 222 (4.36), 282 (3.63), 290 (3.57); λ_{min} 243 (3.07), 288 (3.55); sh. 275 (3.56). - IR.: 3490 (HN), 2940, 1620 (C=O), 1450. - ^{1}H-NMR. (100 MHz): 9.1 (br. *s*, H–N(1')); 7.6-6.8 (*m*, H–C(2'), H–C(4'), H–C(5'), H–C(6'), H–C(7')); 3.8-2.4 (*m*, 2 H–C(10), H–C(11), H–C(6)); 2.2-1.0 (*m*, H–C(5), H–C(8), 2 H–C(1), 2 H–C(2), 2 H–C(3), 2 H–C(4), 3 H–C(12), 3 H–C(13), $COCH_3$); 0.85 (*d*, $J=7$, 3 H–C(9)). - MS.: 340 (M^+, 3, $C_{22}H_{32}N_2O$), 239 (68, $C_{17}H_{21}N$), 210 (100, $C_{13}H_{24}NO$), 168 (90, $C_{11}H_{22}N$), 130 (16).

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